REMARKS

Claims 1-13 and 15-19 remain pending in this application.

The present claims relate, in part, to a method for making a diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient, which comprises:

(a) obtaining sera from said patient;

(b) detecting an antibody for *Fusobacterium varium* in said sera; and

(c) correlating the presence of an antibody for *Fusobacterium varium* in said sera with ulcerative colitis (see Claim 16).

The inventors have discovered that the present method is particularly good for the differential diagnosis of ulcerative colitis.

The rejection of Claims 16-18 under 35 U.S.C. §112, first paragraph, is respectfully traversed.

Although the Examiner has recognized that the specification is enabled for a method of detecting *F. varium* antibodies, the Examiner has continued to maintain that the present application does not enable a method of diagnosis of ulcerative colitis (see page 2, lines 13-15 of the September 3, 2004, Office Action). In an attempt to support this rejection, the Examiner lists several factors that contribute to the diagnosis of a disease or disorder including:

1) the know etiologic agent that causes the disease;

2) the cross-reactivity of multiple microorganisms involved in the disease; and

3) the immunopathogenesis associated with the disease.

However, Applicants note that MPEP §2164.04 defines the test for enablement as:

> "A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

In the present application, Applicants submit that it is well within the purview of the skilled artisan to perform steps (a) and (b) in Claim 16 (e.g., (1) obtaining sera from a patient, and (2) detecting an antibody for *Fusobacterium varium* in said sera). In addition to the basic knowledge possessed by the skilled artisan and the explanation provided in the specification, Applicants previously submitted a copy of Ohkusa et al (*Journal of Gastroenterology and Hepatology*, 2002, **17**, 849-853), which clearly shows how sera are obtained form a patient and subsequently tested for bacterial antibodes using both Western blot and ELISA techniques.

In regard to step (3) of Claim 16 ("correlating the presence of antibody for *Fusobacterium varium* in said sera with ulcerative colitis"), the present specification describes a relationship between butyric acid produced by *F. varium* and ulcerative colitis (see page 4, lines 19-28). In particular, Applicants direct the Examiner's attention to page 4, lines 20-24, which state: "the toxins were analyzed and it was found that they were organic acids produced by *Fusobacterium varium* and that the principal component thereof was identified to be butyric acid. Thus, when butyric acid was injected into the rectum of a mouse, a lesion similar to ulcerative colitis was induced." Therefore, the present specification clearly shows a relationship between *F. varium* and ulcerative colitis.

Furthermore, the Examiner's attention is directed to page 9, lies 13-15, which state: "in ELIZA and immunohistochemistry with *F. varium* proteins an antigen, the mean optical

density and the detection rate were higher for our patients than for subjects with Crohn's disease or other controls." Thus, based on this description, it is well within the purview of the skilled artisan to diagnose that ulcerative colitis is caused by *Fusobacterium varium* when an amount of antibodies for *F. varium* are over a predetermined amount. For example, such a predetermined amount may be an average amount of antibodies in healthy controls ± 2SD (standard deviation) according to common methods. To this end, Figure 2 of Ohkusa et al clearly shows differences in detection of antibodies with ulcerative colitis, Crohn's disease, and in healthy controls.

Accordingly, contrary to the assertions by the Examiner, the presence of *Fusobacterium varium* in sera may be used as a diagnostic marker of ulcerative colitis. As such, as evidenced by the present application coupled with Ohkusa et al (2002), Ohkusa et al (2003), and the knowledge generally available in the art, a person possessing a post-doctoral level of experience may perform the claimed invention and readily appreciate the applicability of the results obtained thereby without undue experimentation.

In view of the foregoing, Applicants submit that the present invention is enabled as defined by 35 U.S.C. §112, first paragraph. Accordingly, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 16-18 under 35 U.S.C. §112, second paragraph, is traversed.

The Examiner has once again reiterated this ground of rejection and has asserted that the claims, as presented, fail to recite essential steps. The Examiner asserts that the alleged essential steps amount to a gap between the steps as claimed. Applicants again note that the steps that are alleged to be missing in Claims 16-18 are inherently embraced by the claims and/or well appreciated by the skilled artisan. The Examiner also points to Example 1 and

asserts that this Example "merely" states that a western blot and an ELISA were performed. However, in the analysis of definiteness, the Examiner is reminded that MPEP §2173.02 states:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and
>
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Applicants note that Western Blotting and ELISA methods do not pose new concepts in the art. In fact, entire treatises have been written on each of these topics and, as such, these methods and what they entail are well appreciated by the skilled artisan and require no further description.

Applicants disagree with the Examiner that essential steps have been omitted. MPEP §2171 defines definiteness as "whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art." In the present application, the Examiner has defined the relative skill in the art to be "post-doctoral level" (see paper number 10, page 5, line 20). As such, the skilled artisan possessing such a high level of skill would recognize the full scope of the claims. In particular, the skilled artisan would appreciate, without further amendment, how to make a diagnosis of ulcerative colitis caused by *Fusobacterium varium* in a patient, which comprises:

(a) obtaining sera from said patient;

(b) detecting an antibody for *Fusobacterium varium* in said sera; and

(c) correlating the presence of an antibody for *Fusobacterium varium* in said sera with ulcerative colitis (see Claim 16).

On page 8 of the Office Action dated September 3, 2004, the Examiner lists several

allegedly omitted essential steps that she believes are not inherent to western blot and ELISA methodologies. These steps include:

1) providing a sample,

2) determining that the target antibody is obtained and not antibodies to a mixture of colonic bacteria,

3) determining the amount of antibody significant to make a diagnosis, and

4) the correlation as to how to diagnose ulcerative colitis using the antibody.

The assertion that these steps have been omitted is untrue and contradictory to the Examiner's assigned level of skill in the art.

The ability of the artisan to practice the claimed invention is directly related to the fact that the alleged omitted steps *are* embraced by the claims as presented. Specifically, alleged omitted steps are inherently embraced by the step for detecting an antibody for *Fusobacterium varium* in said sera. For example, these alleged omitted steps are related to the detection technique as further defined in Claims 17-18. The skilled artisan having "post-doctoral level" skill would readily appreciate preparation steps (i.e., 1) providing a sample..., 2) determining that the target antibody... is obtained and not antibodies to a mixture of colonic bacteria) and the detection limits, and 3) determining the amount of antibody significant to make a diagnosis) associated with Western blotting and/or ELISA methods."

Moreover, Applicants note that the claims do, in fact, specify that a sample is provided (i.e., a "sera from said patient"). As for alleged omitted steps (2) – (3), not only are these steps inherent to Western blot techniques and/or ELISA methods, they amount to controls that are ancillary to the claimed invention.

The Examiner has maintained this ground of rejection again asserting that Example 1 of the specification merely shows that a Western blot and an ELISA were used and poses several questions, including:

1) Were whole *Fusobacterium varium* organisms used to detect antibodies or were proteins of *F. varium* (antigens) used in the assay?

2) Were serum antibodies detected only in patients with UC?

3) Were the antibodies detected in serum from patients with other diseases such as Crohns disease?

4) If (3) is affirmative, were the amounts of antibodies detected in UC patients significantly different from patients with other diseases?

5) How does the detection of antibodies to *Fusobacterium varium* correlate to the diagnosis of UC and not other diseases, if antibodies to *F. varium* were found in patients with other diseases?

6) What is the distinction?

In regard to question (1), such a question further underscores the lack of merit of the present rejection. As would be appreciated by any technician in a laboratory in the relevant art, Western blot techniques typically require an SDS-PAGE separation step followed by electrophoretic transfer of the separated *proteins* from the polyacrylamide gel to a membrane (e.g., nitrocellulose). This method would necessarily exclude the use of whole cells in the detection step. However, it should again be noted that the sample that is to be probed by antibody is the sera of the patient. Whether the whole *F. varium* organisms are used or not is dictated by the detection technique utilized and is not limited. Such a fact is readily apparent both from the claims and the specification.

Questions (2) – (6) appear to relate to the same general idea, which can be summarized as: what controls are present that would distinguish a diagnosis of ulcerative colitis from any other disease when *F. varium* is detected? However, the controls related to

the method are irrelevant in the analysis of whether the claim as written is definite. At best this question relates to one of enablement.

Applicants again submit that with the specification in hand, in particular Example 1 at page 9, the artisan would readily appreciate the scope of present Claims 16-18, as well as the techniques embraced by Western blotting and/or ELISA methods.

In view of the foregoing, Applicants believe that the language of the claims are such that a person of ordinary skill in the art could interpret the metes and bound of the claims so as to understand how to avoid infringement (MPEP §2173.02). Applicants note that this rejection appears to be, at best, because the Examiner merely wants the Applicant to improve the clarity or precision of the language used. However, since the skilled artisan can readily appreciate the meaning of the claims, Applicants submit that further amendments are unnecessary. Therefore, Applicants request withdrawal of the claim rejection pursuant to MPEP §2173.02.

For the foregoing reasons, Applicants submit that Claims 16-18 are in compliance with 35 U.S.C. §112, second paragraph. Withdrawal of this ground of rejection is requested.

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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